201-14593

Celanese Ltd

14 July 2003

The Honorable Christine Todd Whitman
Administrator
U. S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N. W.
Washington, DC 20460

Subject: Revisions/Updates to the Robust Summaries and Test Plan for 1,3-Butanediol (CASNO 107-88-0)

Dear Administrator Whitman,

Celanese Ltd. is hereby responding to the U.S. EPA's comments posted May 13, 2003 on the Chem Right to Know HPV Challenge Web site for the Test Plan and Robust Summaries of 1,3-Butanediol (CASNO 107-88-0).

Celanese Ltd. thanks the EPA for their careful review of the Test Plan and Robust Summaries. Celanese has incorporated most of the changes requested by the EPA. Specific responses to each of EPA comments are given in this letter in italics following a bullet.

The revised Test Plan and Robust Summaries are being transmitted electronically as Adobe pdf documents.

Health Effects

Adequate data were provided for the acute, repeated-dose, and developmental toxicity endpoints for the purposes of the HPV Challenge Program. However, EPA reserves judgement on the genetic toxicity endpoint, pending receipt of an adequate justification for the use of 1,4-butanediol as an analog. The submitter needs to address this and other deficiencies in the robust summaries and significantly revise the robust summary for the 'five-generation' reproductive toxicity study.

- *Response: Additional justification in the form of a complete discussion of the metabolism of these analogs and rationale why these are suitable is provided in the rest plan*

Genetic Toxicity. Although the 1,4-butanediol studies submitted for gene mutations and chromosomal aberrations appear to be well-conducted, the submitter's justification for using analog data for bacterial mutagenicity stated only that 'simple glycols as a class are not known to be genotoxic.' No studies were cited to show that various types of glycols (e.g., 1,2; 1,3; 1,4) are negative in the Ames test. Additional acceptable justification for the use of 1,4-butanediol data might include comparative metabolism information or comparison of general toxicities.

- *Response: The suggested comparative metabolism information was added.*

Reproductive Toxicity. EPA reserves judgment on the 'five-generation' reproductive toxicity study in dietarily-exposed rats pending the submission of additional information in the robust summary. (This study is considered to be the key study because it included multiple dose levels.) The summary omitted the compound purity, methods for evaluating toxicity in parents (e.g., it is not clear whether

the epididymides were analyzed), the specific reproduction and lactation parameters that were measured (e.g., were the number of implantation sites recorded?), and statistical methods. In addition, the summary defined the study type as a 5-generation study, although the summary appears to describe a 3-generation study (5 litters/generation). The similarity of the study to OECD Guideline 416 could not be determined from the information provided.

- *Response: Additional details of the study were added so the reader may compare the design to the current OECD standard. Statistical methods, as far as they are specified have been added o the robust summary. The dosing procedures and levels far exceeded the requirements of an OECD 416; however, the parameters examined were probably not as extensive in this study published in 1981. It is impossible to determine what specific organ systems were examined, as there is not a full description of the examination protocol. As this is a published study, all details available for review are in the open literature and it would be redundant to reproduce all the materials and methods and the data tables in the robust summary. In addition, the critical endpoint for a reproduction study is reproductive performance and not a full description of histopathologic irregularities that did not affect reproductive performance. This is especially true in this study where heroic dose levels were administered with only minimal effects on reproduction.*

Ecological Effects (*fish, invertebrates, and algae*)

The endpoint for algae has been adequately addressed for the purposes of the HPV Challenge Program. However, the justification for using analog data for the fish and invertebrate endpoints has not been clearly stated. In addition, the submitter needs to provide robust summaries for the key fish and invertebrate analog studies before EPA can determine whether these data are adequate.

- *Response: Robust summaries for the analog 1,4-Butanediol were added to the document.*

Fish. The submitter needs to address several discrepancies between the values reported in the test plan and robust summary for the predicted acute fish toxicity of 1,3-butanediol. In the test plan (p. 10) the submitter reported a 96-hour LC50 of 8984 mg/L, but reported a 96-hour LC50 of 9484 mg/L in the robust summary (p. 8). Additionally, these values differed from the predicted value (9494 mg/L) that is provided by ECOSAR (v0.99) when the log Kow for 1,3-butanediol (-0.29) is entered into the program, as was reportedly done by the submitter.

- *Response: The fish LC-50 data in the test plan was a typographical error and was corrected to match the test plan at 9494 mg/L.*

Invertebrates. The submitter reported a predicted 48-hour EC50 of 7344 mg/L in the test plan (p. 10), but 8684 mg/L in the robust summary (p. 8). The submitter explained the derivation of the robust summary value (i.e., entry of the log Kow for 1,3-butanediol into the ECOSAR program); however, it is not clear how the test plan value was derived.

- *Response: The test plan value was corrected*

Specific Comments on the Robust Summaries

Environmental Fate

Biodegradation. The submitter needs to provide a robust summary of the ready biodegradation study described in the test plan (Reference # 11; Huntingdon Life Sciences Limited, 2000).

- *Response: The robust summary for biodegradation was inadvertently omitted when converting from the IUCLID program to Word. It has been added.*

Health Effects

Genetic Toxicity. A robust summary for a negative cytogenetics/chromosomal aberrations assay in rats exposed in a multigenerational feeding bioassay omitted the name and purity of the test material. The submitter needs to indicate whether the animals were adults when the bone marrow was taken; also, the number of animals assessed in each generation is limited (2/sex/dose) compared with OECD Guideline 475, which specifies 5/sex/dose. Despite these deficiencies, the data are acceptable when considered in addition to the chromosomal aberrations study on 1,4-butanediol (if adequate justification is provided for the analog).

- *Response: The age of the animals were added*

Developmental Toxicity. The developmental toxicity data are acceptable. However, the robust summary for a study in rats exposed by gavage omitted the gavage vehicle, maternal necropsy data (if performed), and mortality data.

- *Response: Vehicle was added.*

Ecological Effects

Invertebrates. ECOSAR predicts a 48-hour LC50, not a 48-hour EC50, for this chemical class. Thus, the submitter needs to change "EC50" to "LC50" in the robust summary.

- *Response: The requested change was made.*

Sincerely yours,

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